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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,358	08/11/2006	Austin Gerard Smith	09641.0011-00000	1585

22852 7590 06/12/2009

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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
06/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,358	SMITH ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-38* is/are pending in the application.

4a) Of the above claim(s) *17-27 and 30-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6 and 8-38 as recited in the preliminary amendment filed 4/17/06 with the original application are currently pending.

Election/Restrictions

Applicant's election of Group I, claims 1-6, 28, and 29, in the reply filed on 3/27/09 is acknowledged. Applicant's election of the species "genetically altered to include exogenous DNA" and "LIF" in the same reply is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 17-27 and 30-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/27/09.

Examination on the merits will commence at this time on claims 1-16, 28, and 29 ONLY, as they pertain to the elected species where applicable.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 12-16, 28, and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 requires that the medium of claim 1 be "free of serum extract," which is confusing because it is not clear what compositions are included in the term "serum extract" and which are not. Depending on the extraction conditions, "serum extract" may contain any single component of serum. Clarification is required.

Claim 12 requires culturing the cell in medium containing an Id protein and activating gp130 downstream signaling, but it is not clear whether this activation is a result of the culturing step or whether it represents its own independent positive step. Clarification is required. The examiner suggests that "and" in this phrase be replaced by "thereby" or "and then," depending on the meaning applicant wishes to impart. Because claims 13-16 depend from indefinite claim 12 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 28 is drawn to a method of obtaining "a pluripotent cell," but the steps refer only to "a cell." It is not clear whether the pluripotent cell of the preamble is the same as the cell of the steps or whether it is actually the end product. Clarification is required. Because claim 29 depends from indefinite claim 28 and does not clarify the point of confusion, it must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noguiera et al. (2000, *Biochemical and Biophysical Research Communications* 276: 803-812; on IDS) taken in view of Benezra et al. (1990, *Cell* 61: 49-59; reference U) and Smith et al. (1999, U.S. Patent 5,871,961; reference A).

Noguiera teaches culturing mouse embryonic stem (ES) cells in medium supplemented with LIF (page 804, column 1, under "ES cell culture). Noguiera teaches that cells so cultured remain undifferentiated (page 804, column 2, under "ES cell differentiation").

Noguiera does not teach culturing ES cells with an Id gene product, e.g. an Id protein.

Benezra teaches a cDNA that encodes the inhibitor of differentiation (Id) gene and its product, a helix-loop-helix (HLH) protein (page 50, column 1; and Figure 1). Benezra teaches that Id is downregulated upon differentiation (page 50, column 2) and that transfecting undifferentiated cells with Id cDNA inhibits their differentiation (pages 53-54). Benezra suggests expressing Id in additional cell types (page 54, column 1).

Smith teaches methods for producing recombinant histidine-tagged CR8 (his_6-CR8), a HLH protein, in an *E. coli* expression system and methods for purifying his_6-CR8 on a nickel column (column 73, line 63, through column 74, line 27). Smith teaches that his_6-CR8 protein so produced and isolated retains its ability to bind DNA (column 78, lines 32-56).

A person of ordinary skill in the art would have had a reasonable expectation of success in preparing recombinant Id protein by cloning the Id cDNA taught by Benezra

into the expression vector taught by Smith and recovering purified, active his_6-Id using the method of Smith because both Id and CR8 are HLH proteins; the skilled artisan would have had a further reasonable expectation of culturing ES cells in media containing purified his_6-Id because Smith teaches that purified HLH proteins retain biological activity and are, therefore, suitable for biological systems. The skilled artisan would have been motivated to include purified, active his_6-Id in the medium of Noguiera because Benezra teaches that Id inhibits differentiation, and Noguiera's medium contains LIF, which also inhibits differentiation. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). See M.P.E.P. § 2144.06.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to produce and to purify Id protein as directed by Smith and Benezra and to include such protein in the culturing of Noguiera because combining Id and LIF in a single medium would be expected to maintain the ES cells of Noguiera in an undifferentiated state.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 1, 2, 4-6, and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noguiera taken in view of Benezra and Blackburn et al. (2002, U.S. Patent Application Publication 2002/0146689; reference B).

Noguiera teaches culturing mouse embryonic stem (ES) cells in medium supplemented with LIF (page 804, column 1, under "ES cell culture). Noguiera teaches that cells so cultured remain undifferentiated (page 804, column 2, under "ES cell differentiation").

Noguiera does not teach expressing an Id gene product, e.g. an Id protein, in ES cells.

Benezra teaches a cDNA that encodes the inhibitor of differentiation (Id) gene and its product, a helix-loop-helix (HLH) protein (page 50, column 1; and Figure 1). Benezra teaches that Id is downregulated upon differentiation (page 50, column 2) and that transfecting undifferentiated cells with Id cDNA inhibits their differentiation (pages 53-54). Benezra suggests expressing Id in additional cell types (page 54, column 1).

Blackburn teaches vectors and methods for expressing cDNAs of interest episomally in ES cells (Example 1 at paragraphs 98-126, as well as paragraphs 19, 59-61, and 80). Blackburn's method results in extremely high rates of transfection (paragraph 121) and varying levels of expression (paragraph 124-126).

A person of ordinary skill in the art would have had a reasonable expectation of success in expressing the Id cDNA of Benezra using the system and method of Blackburn in the ES cells of Noguiera because Blackburn teaches that any cDNA may be expressed in ES cells. The skilled artisan would have been motivated to express Id

in the ES cells of Noguiera in order to maintain the ES cells in an undifferentiated state until differentiation is desired; given the teachings of Benezra, the skilled artisan would have had a reasonable expectation that transfecting ES cells with Id would inhibit their differentiation.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to transfect the ES cells of Noguiera with the Id cDNA of Benezra using the expression system and method of Blackburn in order to keep the ES cells in an undifferentiated state by combining the known effects of Id and LIF on ES cell proliferation.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 1-6, 8-16, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noguiera taken in view of Benezra, Smith, Blackburn, and Kaufman et al. (2001, U.S. Patent 6,280,718; reference C).

Noguiera teaches culturing mouse embryonic stem (ES) cells in medium supplemented with LIF (page 804, column 1, under "ES cell culture). Noguiera teaches that cells so cultured remain undifferentiated (page 804, column 2, under "ES cell differentiation").

Noguiera does not teach culturing ES cells with an Id gene product, e.g. an Id protein. Noguiera does not teach expressing an Id gene product, e.g. an Id protein, in ES cells. Noguiera does not teach culturing ES cells in serum-free medium.

Benezra teaches a cDNA that encodes the inhibitor of differentiation (Id) gene and its product, a helix-loop-helix (HLH) protein (page 50, column 1; and Figure 1). Benezra teaches that Id is downregulated upon differentiation (page 50, column 2) and that transfecting undifferentiated cells with Id cDNA inhibits their differentiation (pages 53-54). Benezra suggests expressing Id in additional cell types (page 54, column 1).

Smith teaches methods for producing recombinant histidine-tagged CR8 (his_6-CR8), a HLH protein, in an *E. coli* expression system and methods for purifying his_6-CR8 on a nickel column (column 73, line 63, through column 74, line 27). Smith teaches that his_6-CR8 protein so produced and isolated retains its ability to bind DNA (column 78, lines 32-56).

Blackburn teaches vectors and methods for expressing cDNAs of interest episomally in ES cells (Example 1 at paragraphs 98-126, as well as paragraphs 19, 59-61, and 80). Blackburn's method results in extremely high rates of transfection (paragraph 121) and varying levels of expression (paragraph 124-126).

Kaufman teaches a method for maintaining ES cells in an undifferentiated state by culturing them in medium containing serum-free serum replacement (column 4, lines 35-67, especially lines 47-52).

A person of ordinary skill in the art would have had a reasonable expectation of success in preparing recombinant Id protein by cloning the Id cDNA taught by Benezra into the expression vector taught by Smith and recovering purified, active his_6-Id using the method of Smith because both Id and CR8 are HLH proteins; the skilled artisan would have had a further reasonable expectation of culturing ES cells in media

containing purified his_6-Id because Smith teaches that purified HLH proteins retain biological activity and are, therefore, suitable for biological systems. The skilled artisan would have been motivated to include purified, active his_6-Id in the medium of Noguiera because Benezra teaches that Id inhibits differentiation, and Noguiera's medium contains LIF, which also inhibits differentiation. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). See M.P.E.P. § 2144.06.

A person of ordinary skill in the art would have had a reasonable expectation of success in expressing the Id cDNA of Benezra using the system and method of Blackburn in the ES cells of Noguiera because Blackburn teaches that any cDNA may be expressed in ES cells. The skilled artisan would have been motivated to express Id in the ES cells of Noguiera in order to maintain the ES cells in an undifferentiated state until differentiation is desired; given the teachings of Benezra, the skilled artisan would have had a reasonable expectation that transfecting ES cells with Id would inhibit their differentiation.

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the serum-free medium of Kaufman for the serum-containing medium of Noguiera because both media may be used to maintain ES cells in an undifferentiated state and are, therefore, functional equivalents for each other.

Substituting one for the other would have been obvious at the time of the invention. "When a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1395-1396, quoting *Sakraida v. AG Pro, Inc.,* 425 U.S. 273 (1976).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to culture the ES cells of Noguiera in a serum-free medium as directed by Kaufman containing the LIF of Noguiera and the purified Id suggested by Benezra and Smith in order to keep the ES cells in an undifferentiated state; it would have also been obvious to transfect the ES cells of Noguiera with Id cDNA as taught by Benezra and Blackburn and then to culture the transfected cells in the serum-free medium of Kaufman further containing the LIF of Noguiera for the same reasons. The art establishes that the serum-free medium of Kaufman, the LIF in the medium of Noguiera, and the Id protein of Benezra in view of Smith and Blackburn all have the same explicitly stated utility of inhibiting differentiation in undifferentiated cells, so combining these three components would have been obvious at the time the invention was made.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651